Medical and Pediatric Oncology 29:86–91 (1997)

Systematic Approach for Detection of Endocrine Disorders in Children Treated for Brain Tumors

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Endocrine dysfunction can be challenging to diagnose in children treated for brain tumors. Treatments are available for hormonal replacement and when necessary, hormonal suppression. Without these endocrine treatment regimens, life can be unnecessarily difficult or unpleasant. An endocrine survey can be used to screen at-risk neuro-oncology patients once or twice a year to facilitate the recognition of endocrine dysfunction. It is hoped that through the use of a routine screening program, physicians will be able to diagnose and begin treatment of endocrine problems in a time-efficient manner. Med. Pediatr. Oncol. 29:86–91, 1997.

Key words: pediatric; brain tumor; endocrine

INTRODUCTION

Endocrine dysfunction is a common occurrence in children treated for tumors of the central nervous system. Endocrine problems can occur at many levels within a hormone axis. A hormonal axis consists of central components that include the hypothalamus and pituitary (HP) and endocrine end organs which respond to hormones released from the central nervous system. Hypothalamic and pituitary components of hormonal axes are vulnerable to compression or invasion by the tumor, and intracranial treatments such as surgery and radiation. The endocrine end organs such as the thyroid gland and gonads can be affected by spinal irradiation and chemotherapy required as treatment for the brain tumor. The reported frequency of endocrine abnormalities in children treated for brain tumors is quite variable. It depends on the type and location of the tumor, the age at onset of treatment, the types of therapies directed at the tumor, and the clinician's index of suspicion for endocrine disorders. Six hormone systems regulated by the hypothalamus need to be monitored in pediatric patients treated for brain tumors. They are growth hormone, thyroid hormone, prolactin, adrenal hormones, gonadal hormones and antidiuretic hormone.

Hypothalamic and pituitary hormone deficiencies are common after central nervous system (CNS) irradiation. The radiation-induced disruption of the hormonal axes within the central nervous system is thought to occur at the level of the hypothalamus rather than the pituitary gland [1,2]. Constine et al. [3] studied 32 children and adults who had received HP radiation (average dose was 54 Gy) as part of their brain tumor treatment and found that 28% had one HP hormone deficiency, 25% were lacking two HP hormones, an additional 25% were lacking three HP hormones, and 12% lacked four HP hormones. Only 9% of those tested had all the hormone axes intact [3]. In children who have received radiation to the HP region, the most common form of endocrine dysfunction is growth hormone (GH) deficiency [4], and gonadal abnormalities are the next most frequent form of hypothalamic pituitary axis disruption. Growth hormone deficiency has been reported after central nervous system doses as low as 18 Gy [5,6], while the production of adrenal hormones, thyroid hormones and prolactin are usually not affected until HP irradiation doses exceed 30 Gy [7].

Chemotherapy may also lead to endocrine dysfunction. The effect of adjuvant chemotherapy on growth was addressed by Olshan et al. [8] in pediatric patients treated for medulloblastoma. They studied growth patterns from diagnosis to 4 years after diagnosis in 38 patients [8]. There was significant impairment of growth during years 1, 2 and 4 in children treated with surgery, radiation therapy and chemotherapy compared to children treated with surgery and radiation therapy alone. This observation suggests a lasting effect of chemotherapy on growth beyond the acute chemotherapy treatment phase. Thyroid dysfunction after treatment for cancer has been primarily

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Contract grant sponsor: Genentech Inc.

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Received 19 January 1996; Accepted 10 May 1996

TABLE I. Disorders Identified Through an Endocrine Survey in Children Treated for Brain Tumors*

I.	Short stature
	A. Poor growth due to poor nutrition
	B. Poor growth due to spinal irradiation
	C. Growth hormone deficiency
	D. Hypothyroidism
II.	Hypothyroidism
	A. Primary hypothyroidism
	B. Compensated hypothyroidism
	C. Central hypothyroidism
III.	Elevated prolactin
	A. Hyperprolactinemia
	B. Hypothyroidism
IV.	Adrenal insufficiency
	A. Central adrenal insufficiency
	B. Iatrogenic adrenal insufficiency
V.	Alterations in puberty
	A. Precocious puberty
	B. Delayed puberty
	C. Primary gonadal failure
	D. Central hypogonadism
VI.	Fluid and electrolyte imbalance
	A. Diabetes insipidus
	B. Syndrome of inappropriate antidiuretic hormone
	C. Cerebral salt wasting

*Endocrine disorders frequently seen in children who are treated for brain tumors and other disorders that can mimic endocrine disease.

linked to radiation therapy but there may be deleterious effects of adjuvant chemotherapy on thyroid hormone production as well [9]. Chemotherapeutic drugs, specifically alkylating agents, have a well-recognized role in gonadal dysfunction in males and females [10–12].

Lastly, dysfunction in all of the hormone axes must be particularly considered when the tumor is located in the region of the hypothalamus and pituitary. Endocrine dysfunction can be due to compression by the tumor and/or invasion by the tumor. In addition surgical resection in this area can also lead to hormonal deficiencies.

Hormonal deficiencies can significantly impair the lives of survivors of pediatric brain tumors [13]. While hypothyroidism and adrenal insufficiency can be life-threatening, growth hormone deficiency combined with impaired spinal growth or precocious puberty can result in short stature which can be so severe that it is difficult to lead a normal adult life, i.e., drive a car, reach cabinets and counters. Table I depicts several endocrine problems frequently encountered in children who have been treated for brain tumors. If these endocrine disorders are not looked for prospectively in an organized and systematic fashion, they may go undetected or be identified too late for therapeutic intervention.

ENDOCRINE SURVEY

We participate in a multidisciplinary pediatric neuro-oncology clinic and our approach to surveillance for endocrine abnormalities in this patient population will be presented. For each hormone system, a list of signs and symptoms will be described which, when found, may suggest hormonal disturbances. We will also discuss nonendocrine disorders which may initially appear to be endocrine dysfunction. It is important to note that when evaluating pediatric neuro-oncology patients for endocrine problems, we are most often looking for hormone deficiencies. This is the case in all but two hormone systems. The first nondeficient neuroendocrine abnormality is hyperprolactinemia. Prolactin secretion is normally under inhibitory control. When there is disruption of the hypothalamic-pituitary axis, the inhibition is lost and this results in elevated prolactin levels. The second nondeficient neuroendocrine problem is precocious puberty. A child with precocious puberty produces normal amounts of sex hormones but at an inappropriately early age. We will now address each component of the endocrine survey individually.

Growth Hormone

Short stature is the most common endocrine complaint in children with brain tumors, which results in consultation with an endocrinologist. Often help is sought too late when growth plates are beginning to fuse. If pediatric patients with brain tumors are monitored closely with annual anthropometric measurements, growth problems will be detected early when intervention will be most beneficial. In general, three types of abnormally slow growth patterns are observed in this group of patients.

The first pattern involves slowing of growth immediately after diagnosis. This is frequently accompanied by poor weight gain. This pattern typically occurs during the acute phase of therapy and reflects poor caloric intake. Growth velocity improves as appetite and caloric intake improve. The second abnormal pattern of growth reflects disproportionately poor spinal growth after radiation of the spine [14]. Adequacy of growth hormone production is supported by good growth of lower limbs as documented through lower segment measurements and good growth of upper limbs as reflected by arm span measurements. Neither of the first two examples of abnormal growth will benefit from hormone treatment. The third pattern of growth seen in children with brain tumors reflects true growth failure. The child's height percentile on growth charts progressively falls farther and farther below prediagnosis growth percentiles, and the linear growth rate is suboptimal for age. In this growth pattern, the legs and arm span also fail to grow at a normal rate. This pattern of growth is compatible with hormonal deficiency and can be seen in both hypothyroidism and GH deficiency. Hypothyroidism is corrected through the administration of L-thyroxine. In GH deficiency, replacement therapy will be beneficial in the short run to im-

prove height percentiles and in the long run to improve final adult height.

A growth survey includes measurements of weight, standing height, sitting height, lower segment and arm span measurements. Nutritional evaluation and laboratory tests should be obtained on an individual basis. If a child demonstrates declining height percentiles, poor arm span growth, and/or a growth rate less than the 25th percentile (determined by using a height velocity for age growth chart), endocrine laboratory investigation is warranted [15]. Pertinent tests include measurements of insulin-like growth factor I (IGF-I), insulin-like growth factor binding protein 3 (IGF-BP3), bone age determination [16], and a growth hormone stimulation test.

Endocrinologists differ with respect to the best diagnostic test for growth hormone deficiency in this patient population. Some endocrinologists prefer to directly test hypothalamic/pituitary growth hormone production in response to a stimulus using standard GH provocative tests [17]. Others rely on anthropometric data, a declining growth rate combined with decreased serum IGF-BP3 and IGF-I levels [18]. Although low IGF-BP3 levels are sometimes useful in the general population in detecting GH deficiency, its value has come under question in children who are treated for brain tumors [19,20]. If an individual is diagnosed with growth hormone deficiency, recombinant human growth hormone (rhGH) is available for therapy. A full discussion of possible side effects of growth hormone therapy should take place. Data should be presented which supports the lack of increased risk of tumor recurrence during GH therapy [21]. It should also be mentioned that it is unclear whether GH further increases the risk of development of leukemia as a second malignancy in this population that may be already predisposed to develop leukemia by genetic factors or tumor therapy [22]. Growth hormone is given as a subcutaneous injection six times a week. The cost of hormone replacement is on the order of $20,000 per year (for a 30-kg child).

Thyroid Hormone

Many of the symptoms and signs of hypothyroidism are not specific. Obvious symptoms of hypothyroidism such as myxedema, short stature, bradycardia and constipation usually lead to endocrine evaluation. Milder symptoms of hypothyroidism such as lethargy, cold intolerance and increased sleep are less specific and are often seen in euthyroid individuals undergoing cancer treatment. Therefore, routine laboratory monitoring of thyroid function is necessary to diagnose thyroid abnormalities in this patient population. Primary hypothyroidism is common in patients who have received craniospinal irradiation and even more common following combined radiation and chemotherapy [23]. Patients with primary hypothyroidism have a low free T4 and an elevated thyroid stimulating hormone (TSH). The presence of a high TSH level with a normal free T4 value indicates compensated hypothyroidism. This represents an early stage of thyroid failure and should be treated with hormonal replacement. In secondary or central hypothyroidism, symptoms of hypothyroidism tend to be milder. Serum-free T4 is low but TSH is not elevated in response to the decreased free T4 level. Central hypothyroidism can be confirmed with the observation of impaired or delayed TSH response to thyrotropin releasing hormone (TRH) stimulation [17]. Annual screening labs for hypothyroidism include serum free T4 and TSH levels.

Thyroid hormone replacement involves taking L-thyroxine by mouth once a day. Free T4 levels are checked once or twice a year and should be maintained in the upper half of the normal range. The cost of hormone replacement is approximately $150 per year.

Prolactin

Elevated serum prolactin levels can be seen after disruption of the hypothalamic pituitary axis and in primary hypothyroidism. Hyperprolactinemia is more common in women than in men and after high doses of irradiation (>50 Gy) to the HP axis [24,25]. Prolactin levels increase when there is loss of the inhibitory effects of dopamine. In addition, elevation of TRH levels in response to thyroid gland failure stimulates the release of TSH and prolactin from the pituitary gland. Hyperprolactinemia can cause amenorrhea, galactorrhea and decreased libido. Treatment of hyperprolactinemia is not common in the pediatric population, but levels can be lowered through the use of Bromocriptine or other dopamine agonist.

Adrenal Hormone

Symptoms of adrenal insufficiency include poor weight gain, lethargy, failure to thrive, rapid dehydration, shock and death. Fortunately, central adrenal insufficiency is uncommon in children treated for brain tumors. On the other hand, adrenal suppression after prolonged steroid use is a frequent finding in patients who are treated with high dose glucocorticoids. The patient who is emerging from a period of iatrogenic glucocorticoid excess may not be able to produce normal amounts of cortisol. They may have symptoms of adrenal insufficiency despite a Cushingoid appearance. Surgery or illness during this time may provoke an adrenal crisis.

If glucocorticoids have been administered for more than 7 days, we suggest beginning hydrocortisone at a maintenance dose of 10–15 mg/m^2 body surface area/day. The hydrocortisone dose is divided into once or twice a day dosing. Once on maintenance hydrocortisone, the child should be weaned from the high dose glucocorticoids as quickly as is neurologically tolerated. Once maintenance hydrocortisone is the only glucocorticoid given, this dose can be slowly weaned to allow

adrenal recovery. The length of time required for full adrenal recovery may equal the period of time the adrenal glands were suppressed by exogenous glucocorticoids. Stress coverage, which is typically 3–5 times maintenance, should be provided until full adrenal recovery is documented. Once 2 weeks have passed during which no glucocorticoids (maintenance or stress) are given, the patient's adrenal function can be tested with an ACTH stimulation test, 8 A.M. Cortisol level or a Metyrapone test [26]. All of these tests have their shortcomings, ranging from incomplete information regarding the function of the entire adrenal axis to degree of difficulty in performing the test. We have therefore ranked the tests in our order of preference regarding use. If the response to these tests demonstrate adrenal recovery, hydrocortisone therapy including stress coverage can be discontinued.

Gonadal Hormone

The gonadal axis abnormalities seen in children treated for brain tumors include precocious puberty, delay in onset of puberty and hypogonadism. Precocious puberty is defined as the presence of breast budding before age 8 in girls or testicular enlargement before age 9 in boys. Delayed puberty can be physiological or reflect failure of the gonadal axis. It is defined as lack of signs of puberty by age 13 in girls or age 14 in boys.

Precocious puberty is frequently seen in a variety of intracranial disturbances. Children with precocious puberty demonstrate rapid growth rates in addition to signs of secondary sexual characteristics. Precocious puberty can lead to many psychosocial problems as a result of premature sexual development, accelerated growth as a child and adult short stature. Although in the beginning the growth spurt associated with precocious puberty may preserve or increase prediagnosis height percentiles, early gonadal hormone production can result in adult short stature due to accelerated skeletal maturation and premature closure of growth plates. Prevention of adult short stature due to precocious puberty occurs when interventions to stop puberty are instituted before the child is 6 years old [27]. Often precocious puberty and GH deficiency coexist in children treated for brain tumors. The GH deficiency may not be suspected since the growth rate does not decline, but instead the growth rate may remain stable or accelerate under the influence of sex hormones. Without recognition and treatment of the GH deficiency, the child will not have the benefit of a pubertal growth spurt and will fall short of his/her adult predicted height. It is prudent to evaluate the GH axis when evaluating a pediatric brain tumor patient for precocious puberty. The evaluation of a neuro-oncology patient with precocious puberty includes: a GnRH stimulation test with serial measurement of luteinizing hormone (LH) and follicle-stimulating hormone (FSH), bone age, and in girls an estradiol level and perhaps a pelvic ultrasound, and in boys a testosterone level and a B-hCG level. In addition, an evaluation of the GH axis should be done to determine whether there is coexisting GH deficiency. Central precocious puberty can be suppressed through the use of a gonadotropin releasing hormone (GnRH) agonist. We most commonly use a preparation that is given intramuscularly every 4 weeks. Medication costs are roughly $8,000 per year.

An unusual form of precocious puberty can be seen in boys who have brain tumors and is due to the increased production of human chorionic gonadotropin (hCG) by germ cell tumors. The hCG protein binds to LH receptors on the Leydig cells in the testes and stimulates testosterone production. Precocious puberty will resolve when the hCG levels return to normal.

Lack of puberty can be due to delayed onset of puberty or due to permanent hypogonadism. Initial evaluation for hypogonadism includes bone age, LH, FSH and estradiol or testosterone. Three causes of late puberty will be described. The first cause of late puberty is constitutional delay. Constitutional delay is a normal variant pattern of growth and is frequently seen in children who have had a severe or chronic illness. These children can be thought of as ''late bloomers'' who begin puberty when their bone age approaches 11–12 years. No treatment is required for this cause of delayed puberty. A second cause of delayed puberty is primary (hypergonadotropic) hypogonadism. This condition is due to ovarian or testicular failure and can be seen after chemotherapy, gonadal irradiation or gonadectomy. In this situation, sex hormone levels are low and the LH and FSH levels are elevated. The third cause of delayed puberty is central hypogonadism. With central (hypogonadotropic) hypogonadism there is loss of secretion of LH and FSH to stimulate the gonads to produce sex hormones. Children with hypogonadotropic hypogonadism and those with hypergonadotropic hypogonadism should both receive replacement hormones at an appropriate skeletal age. Female hormones can be replaced by conjugated estrogen in doses that gradually increase over 2 years and then menstrual cycling is achieved by the addition of medroxyprogesterone acetate. Male hormones can be replaced through gradually increasing monthly doses of intramuscular injections of testosterone cypionate or testosterone enanthate. Testosterone therapy through the use of transdermal patches may be an option. Cost for hormone therapy is about $50 per year for males and $250 per year for females.

Antidiuretic Hormone

Antidiuretic hormone (ADH) deficiency and excess are most frequently seen at the time of diagnosis of the brain tumor or after neurosurgery. ADH deficiency which can be seen with perisellar and midline tumors results in diabetes insipidus with polyuria and polydipsia.

TABLE II. Endocrine Survey*

	History physical	Screening lab tests	Diagnostic lab tests	Hormone replacement
Growth hormone	weight standing ht arm span sitting ht lower segment	IGF-BP3 Bone age	GH stimulation test Nutrition evaluation IFG-I Chemistry panel	Recombinant human GH subcutaneous 6 nights/week
Thyroid hormone	heart rate weight height	Free T4 TSH	TRH stimulation test	Thyroxine oral once a day
Adrenal hormones	height weight blood pressure	8 AM Cortisol stress Cortisol	ACTH stimulation test Metyrapone test	Hydrocortisone oral 2–3 times a day Stress coverage = 3–5 times maintenance
Puberty				
Early	Tanner stage height	E2 or testosterone Pelvic ultrasound B-hCG Bone age	GnRH stimulation test	GnRH agonist IM every 4 weeks
Delayed	Tanner stage height	LH and FSH E2 or testosterone bone age	GnRH stimulation test	Females, oral estrogen/progesterone Males, testosterone IM every 4 weeks
ADH				
Diabetes Inspidus	polyuria polydipsia	intake: output serum sodium serum omolality urine sodium urine osmolality	water deprivation test	Desmopressin acetate Intranasal once or twice a day
SIADH	oligouria			Fluid restriction

*Endocrine survey information to be obtained for each of the six hormone systems in the history, physical examination, screening laboratory tests, and diagnostic laboratory test. A brief description of what is involved in treatment of endocrine disorders is included. IGF-BP3, insulin-like growth hormone binding protein 3; GH, growth hormone; IFG-I, insulin-like growth factor I; T4, thyroxine; TSH, thyroid stimulating hormone; TRH, thyrotropin releasing hormone; ACTH, adrenocorticotropin hormone; E2, estradiol; B-hCG, beta human chorionic gonadotropin; GnRH, gonadotropin releasing hormone; IM, intramuscular; LH, luteinizing hormone; FSH, follicle-stimulating hormone.

Affected patients have excessive urination often despite elevated serum sodium and increased serum osmolality. A diagnostic test is the water deprivation test with measured response to ADH [17]. Diabetes insipidus can be treated using an intranasal spray of Desmopressin acetate once or twice daily. The annual cost for desmopressin acetate (2 puffs per day) averages $1,000.

The syndrome of inappropriate ADH excretion (SIADH) is usually transient and typically occurs during acute alterations of the central nervous system such as brain swelling or hemorrhage. Clinically, SIADH is characterized by hyponatremia, increased intravascular volume and an inappropriately high urine osmolality. The treatment of SIADH is fluid restriction.

Cerebral salt wasting also needs to be considered in the clinical setting of hyponatremia. This entity has been described in neurosurgical patients who have hyponatremia and volume depletion [28,29]. Patients can secondarily develop increased ADH levels in response to the hypovolemia. Treatment for this disorder is volume expansion and sodium supplementation [30].

Summary

Children treated for brain tumors who are at risk should have endocrine evaluation once or twice a year. Children who are at risk are those who have tumors in the HP region, those who have received cranial irradiation and any child with a brain tumor who is having symptoms or showing signs of endocrine abnormalities. At our institution, we achieve this by having a pediatric endocrinologist participate in our multidisciplinary pediatric neuro-oncology clinic. If an endocrinologist is not available for regular participation in such a clinic, a detailed protocol with screening questions in the history, specific points to be assessed in the physical examination and screening laboratory tests as described in this paper can be used by other individuals following the patients. If there is any deviation from normal on the endocrine

screen a consultation with a pediatric endocrinologist may be warranted. Measurements to be made at visits include: vital signs, standing height, weight, lower segment/sitting height, arm span and Tanner stage for puberty. Annual labs include a free T4, TSH and 8 AM cortisol. Other tests to obtain when clinically indicated include: IGF-BP-3, IGF-I, bone age x-ray, gonadotropins, sex hormones, prolactin and measures of water balance. More extensive endocrine testing may be needed if screening labs are abnormal. Table II outlines the different components of the endocrine survey. From the endocrine survey, data can be collected prospectively and serial information can be tracked in a database. This screening system, or endocrine survey, used regularly will allow early detection of endocrine abnormalities and timely therapeutic intervention.

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